JACC Vol. 20, No. 4
October 1992:854–7

Editorial Comment

Endothelin and the Vascular Choir in Heart Failure*

LYNNE WARNER STEVENSON, MD, FACC,
GREGG C. FONAROW, MD
Los Angeles, California

Advanced heart failure is characterized by alterations in vascular tone and response that may further compromise perfusion, organ function and survival. The sympathetic nervous system, the renin-angiotensin system, natriuretic peptides, vasopressin and cytokines can all influence vascular tone under certain conditions. Originally regarded as part of the audience, the endothelium has recently been recognized to participate actively in this choir through synthesis and release of relaxing factors, prostaglandins and endothelin (Fig. 1).

Physiologic effects of endothelin and endothelin receptors. Endothelin, a 21-amino acid peptide first described by Yanagisawa et al. (1), is the most potent vasoconstricting substance known for the vascular smooth muscle of both arteries and veins. Of the three endothelins described, endothelin-1 has been the best characterized (2). Stimuli for release from endothelial cells include norepinephrine, vasopressin, thrombin, transforming growth factor beta and interleukin-1. Regulation is primarily at the level of message transcription, and the regulatory region of human preproendothelin-1 gene has been shown to contain sequences influenced by other acute phase reactants. Release and cleavage of the big endothelin to active endothelin may be further sites of regulation.

Endothelin receptors have been found in the heart and kidney as well as blood vessels. There are at least two receptor types for endothelin (2). Endothelin-A receptors are on smooth muscle cells. Endothelin mobilizes intracellular calcium release, stimulated by inositol triphosphate. Extracellular calcium entry contributes to the more sustained contractions. Voltage-dependent calcium channels are involved and adenosine triphosphate (ATP)-sensitive potassium channels also may be stimulated by endothelin (3). Through endothelin-B receptors on endothelial cells, phospholipase A_2 is stimulated and the vasodilator prostacyclin is synthesized. These two endothelin actions cause the biphasic response that can be seen after exogenous administration in animals. The initial brief vasodilator component appears to result from endothelin stimulation of prostacyclin production and can be blocked by cyclooxygenase inhibitors. The subsequent prolonged vasoconstriction can function to conserve blood flow to the heart and brain, at the expense of the kidney and liver.

Isolation of physiologic effects of endothelin in vivo is complicated. In addition to direct vascular effects, endothelin can act in concert with other regulatory systems. Infusions in dogs can increase circulating levels of atrial natriuretic factor, vasopressin and aldosterone (4). Renin release has been variously found to be stimulated or depressed (5,6), which may depend in part on the degree of concomitant atrial natriuretic factor stimulation. Aldosterone appears to be directly stimulated through endothelin receptors on the zona glomerulosa. These other regulatory systems also can effect endothelin action, because angiotensin II, vasopressin and endothelin itself downregulate the endothelin-A receptors on smooth muscle cells (3). Clearance of endothelin may vary among animals and among disease states. Whereas endothelin is cleared predominantly in the lungs of rats (7), it is cleared through both the lungs and the kidneys of dogs. In a dog study of pacing-induced heart failure, baseline endothelin levels were elevated threefold and exogenous administration of endothelin to dogs with heart failure caused a greater increment in endothelin concentration but less effect on vasoconstriction and renal blood flow than in control dogs (4).

Role of increased endothelin in disease states. The contribution of endothelin to the human circulation has not been established. In normal volunteers, detectable levels of endothelin circulate normally, increase with upright tilting and cold exposure and decrease after saline infusion in parallel with plasma renin activity (8–10). The current study by Lerman et al. (11) demonstrated a twofold increase in plasma endothelin-1 levels in patients with class III and IV heart failure. Simultaneous studies of other patients with heart failure confirm significant elevations compared with levels in normal control subjects; however, normal levels have varied almost threefold from study to study, and this variation may reflect differences in sampling site as well as variations in the specificity of the endothelin antibodies employed for the radioimmunoassay (8–13). The degree of elevation of plasma endothelin level in patients with heart failure ranges from twofold, as reported by Lerman et al. (11) and by McMurray et al. (13) and Cody et al. (12), to fivefold, as reported by Stewart et al. (8). Patients whose heart failure was associated with pulmonary hypertension had higher levels than those of other patients with heart failure (12). Elevated

*Editorials published in *Journal of the American College of Cardiology* reflect the views of the authors and do not necessarily represent the views of JACC or the American College of Cardiology.

From the Ahmanson-UCLA Cardiomyopathy Center, Division of Cardiology, University of California, Los Angeles School of Medicine, Los Angeles, California. Dr. Stevenson is a Clinician-Scientist of the American Heart Association, Greater Los Angeles Affiliate, Los Angeles, and is also supported by the Eastern Star Foundation, Los Angeles, and the Helen Wolfe Estate in memory of Peter D. Wolfe, Los Angeles. Dr. Fonarow is supported by Training Grant 1T32HL07412-10 from the National Institutes of Health, Bethesda, Maryland.

Address for correspondence: Lynn Warner Stevenson, MD, Division of Cardiology, University of California, Los Angeles, 47-123 CHS, 10833 Le Conte Avenue, Los Angeles, California 90024-1679.

0735-1097/92/$5.00

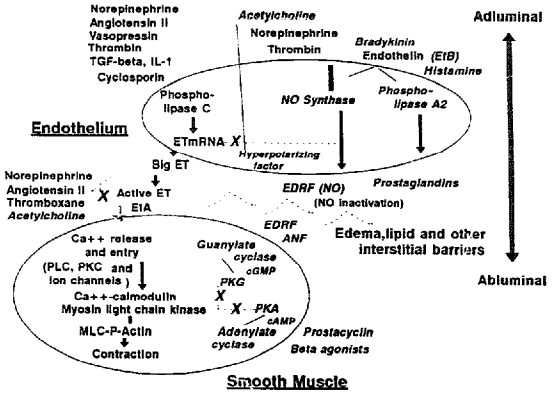

Figure 1. Voices in the vascular choir: the interaction between circulating and local factors in vasodilation and vasoconstriction. Components in **italics** indicate predominant vasodilators. **Dotted** lines intercepted with an **X** indicate a negative or inhibitory influence, such as that from norepinephrine and angiotensin II, which directly stimulate contraction but also cause down-regulation of endothelin receptor A (EtA) receptors. ANF = atrial natriuretic factor; CA++ = calcium ion; cAMP = cyclic adenosine monophosphate; cGMP = cyclic guanosine monophosphate; EDRF = endothelium-derived relaxing factor; ET = endothelin; EtB = endothelin receptor B; IL-1 = interleukin-1; MLC = myosin light chain; mRNA = messenger ribonucleic acid; NO = nitric oxide; P = phosphate; PKA, PKC, PKG = protein kinase A, C and G, respectively; PLC = phospholipase C; TGF-beta = transforming growth factor beta.

endothelin levels have also been found in patients with primary pulmonary hypertension (14) and in patients with pulmonary hypertension secondary to congenital heart disease (15). Other conditions that have been associated with elevated endothelin levels are acute myocardial infarction (16,17) and abdominal surgery (18).

This study also demonstrates that endothelin levels are elevated after heart transplantation. Cyclosporine given at high doses to rats caused increased endothelin levels and renal dysfunction that could be prevented by administration of anti-endothelin antibodies (19). Cyclosporine also results in an increase in sympathetic nerve traffic in humans, which could stimulate increased endothelin release (20). The differences between findings in the current study of 8 patients and those of the study of Edwards et al. (21), in which 24 heart transplant patients with and without cyclosporine therapy had normal endothelin levels, remain unexplained. The elevated endothelin levels seen early after heart transplantation may reflect the general stress of surgery, because high endothelin levels have been found after major abdominal surgery (18). At extended periods after transplantation, a greater degree of hypertension and renal dysfunction may have contributed to elevated levels in the current study.

Role of endothelin in heart failure. The results of this study suggest that endothelin may contribute to the circulatory derangement of heart failure. However, detected levels of circulating endothelin may not necessarily indicate the physiologic contribution of this hormone. "Big" endothelin, which is inactive until converted, is recognized in most assays, which will thus overestimate the active endothelin. The cross-reactivity of the antibody in this study was <37% with big endothelin. The specific "sandwich" immunoassays performed by Miyauchi et al. (17) showed active endothelin-1 levels to be in the range of 1 pg/ml, which is lower than that reported in less specific assays, and showed big endothelin to be normally present at twice the concentration of endothelin-1. In disease states the conversion of big endothelin could conceivably be impaired so that more inactive hormone would be detected. The amount of release into the circulation from the endothelium may be a small fraction of the active endothelin released abluminally to the smooth muscle cells, representing a "spillover" analogous to that of norepinephrine from sympathetic nerve terminals. Impaired pulmonary and renal clearance of endothelin, which might be expected in congestive states, may elevate levels despite normal local release. In addition, the effect of elevated endothelin levels can be reduced by downregulation of endothelin receptors (2). In the paced dog with heart failure, exogenous endothelin caused less systemic and renal vasoconstriction than in the control dog (4).

What is the significance of endothelin elevation in heart failure? In this study, there were no correlations between hemodynamic variables and the degree of elevation, which was also reported by Cody et al. (12). However in the patients studied by Cody et al. (12), the level of endothelin elevation did not correlate with systemic vascular resistance or cardiac output in human heart failure, but it did reflect the degree of elevation of intracardiac filling pressures, which has been suggested to be the most critical hemodynamic variable for both clinical function and prognosis once advanced heart failure is present (22,23). Does endothelin elevation represent a cause or an effect of decompensation?

JACC Vol. 20, No. 4
October 1992:854–7

It has been shown that comparable levels may cause modest systemic vasoconstriction in normal control patients. In the study of Vierhapper et al. (24), doses between 1 and 2.5 ng/kg per min resulted in levels of 10 to 20 pg/ml, which elevated mean arterial pressure by 4 mm Hg, but even higher doses did not cause changes in plasma renin, aldosterone or atrial natriuretic factor. Kiowski et al. (25) demonstrated that very low doses caused forearm vasodilation, whereas 25 to 50 ng/min per 100 ml forearm tissue increased local vascular resistance. It is not easy to determine what levels are relevant to pathophysiologic conditions because local release could cause concentrations many times higher than those circulating. However, when baseline endothelin levels are elevated, as in heart failure, the response to further endothelin elevations can be blunted (4). It is not known to what extent inhibition of endothelin activity will directly improve hemodynamic status. Although the vasoconstrictor action of endothelium in vivo may be inhibited by calcium channel blocking agents (25), these agents have not provided major benefit in heart failure. It may be that any hemodynamic benefits of endothelin inhibition will be for reversal of secondary pulmonary hypertension or for preservation of threatened renal function, rather than for systemic vasodilation.

Long-term effects of endothelin. More intriguing than the potential for direct vasodilation is the possibility that endothelin may have more long-term effects on both the heart itself and the neurohumoral activation that appears to contribute to the progression of heart failure. Progression of early left ventricular dysfunction has now been shown to be decreased by angiotensin-converting enzyme inhibitors (26,27). Endothelin messenger ribonucleic acid (mRNA) has been demonstrated in human cardiac tissue, and anti-endothelin antibodies have limited infarct size in a rat model (28). Once hemodynamic compromise at rest has developed, therapy for heart failure has been most effective when hemodynamic improvement can be combined with inhibition of neurohumoral stimulation (29). In normal patients during infusion of endothelin, renin, aldosterone and atrial natriuretic factor levels were not altered (24). However, in dogs with pacing-induced heart failure, endothelin decreased plasma renin activity (4). Blockade of endothelin thus could be deleterious, advantageous or of no obvious effect, depending on the role of endothelin in the neurohumoral axis of patients with heart failure.

Conclusions. The studies of endothelin in patients, such as reported in this issue of the Journal, are critical for the demonstration that endothelin is abnormal in heart failure and after heart transplantation. Endothelin has taken its place as another voice among the growing choir of circulatory regulation. Future investigation will be directed to determine whether this elevation represents a true increase in endothelin activity, causes significant regional or systemic vasoconstriction and represents an adaptive or a deleterious response in these disease states. Such investigation will ultimately determine whether intervention directed against endothelin production and action will provide a new option for therapy of the abnormal circulation.

References

1. Yanagisawa M, Kurihara H, Kimura S, et al. A novel potent vasoconstrictor peptide produced by vascular endothelial cells. Nature 1988;323:411–5.
2. Masaki T, Kimura S, Yanagisawa M, Goto K. Molecular and cellular mechanisms of endothelin regulation: implications for vascular function. Circulation 1991;84:1457–68.
3. Miyoshi Y, Nakaya Y, Wakatsuki T, et al. Endothelin blocks ATP-sensitive K^+ channels and depolarizes smooth muscle cells of porcine coronary artery. Circ Res 1992;70:612–6.
4. Cavero PG, Miller WL, Heublein DM, Margulies KB, Burenett JC. Endothelin in experimental congestive heart failure in the anesthetized dog. Am J Physiol 1990;259:F312–7.
5. Miller WL, Redfield MM, Burnett JC. Integrated cardiac, renal and endocrine actions of endothelin. J Clin Invest 1989;83:317–20.
6. Matsumura Y, Naksae K, Ikegawa R, Hayashi K, Ohyama T, Morimoto S. The endothelium-derived vasoconstriction peptide endothelin inhibits renin release in vitro. Life Sci 1989;44:149–57.
7. de Nucci G, Thomas R, D'Orleans-Juste P, et al. Pressor effects of circulating endothelin are limited by its removal in the pulmonary circulation and by the release of prostacyclin and endothelium-derived relaxing factor. Proc Natl Acad Sci 1988;85:9797–800.
8. Stewart DJ, Cernacek P, Costello KB, Rouleau JL. Elevated endothelin-1 in heart failure and loss of normal response to postural change. Circulation 1992;85:510–7.
9. Lerman A, Hildebrand FL, Aarhus LL, Burnett JC. Endothelin is a vasoconstrictor at physiologic concentrations (abstr). Am J Hypertens 1990;3(suppl A):97A.
10. Margulies KB, Hildebrand FL, Lerman A, Perlla MA, Burnett JC. Increased endothelin in experimental heart failure. Circulation 1990;82:2226–30.
11. Lerman A, Kubo SH, Tschumperlin LK, Burnett JC Jr. Plasma endothelin concentrations in humans with end-stage heart failure and after heart transplantation. J Am Coll Cardiol 1992;20:849–53.
12. Cody RJ, Haas GJ, Binkley PF, Caper Q, Kelley R. Plasma endothelin correlates with the extent of pulmonary hypertension in patients with chronic congestive heart failure. Circulation 1992;58:504–9.
13. McMurray JJ, Ray SG, Abdullah I, Dargie HJ, Morton JJ. Plasma endothelin in chronic heart failure. Circulation 1992;85:1374–9.
14. Stewart DJ, Levy RD, Cernacek P, Langleben D. Increased plasma endothelin-1 in pulmonary hypertension: marker or mediator of disease? Ann Intern Med 1991;114:464–9.
15. Yoshibayashi M, Nishioka K, Nakao K. Plasma endothelin concentrations in patients with pulmonary hypertension associated with congenital heart defects. Circulation 1991;84:2280–5.
16. Stewart DJ, Kubac G, Costello CB, Cernacek P. Increased plasma endothelin-1 in the early hours of acute myocardial infarction. J Am Coll Cardiol 1991;18:38–43.
17. Miyauchi T, Yanagisawa M, Tomizawa T, et al. Increased plasma concentrations of endothelin-1 and big endothelin-1 in acute myocardial infarction. Lancet 1989;2:53–4.
18. Saito T, Yanagisawa M, Miyauchi T, et al. Endothelin in human circulating blood: effect of major surgical stress (abstr). Jpn J Pharmacol 1989;49:215.
19. Kon V, Sugiura M, Inagami T, Harvie BR, Ichikawa I, Hoover RL. Role of endothelin in cyclosporine-induced glomerular dysfunction. Kidney Int 1990;3:1487–91.
20. Scherrer U, Vissing SF, Morgan BJ, et al. Cyclosporine-induced sympathetic activation and hypertension after heart transplantation. N Engl J Med 1990;323:693–9.
21. Edwards BS, Hunt SA, Fowler MB, Valantine HA, Anderson LM, Lerman A. Effect of cyclosporine on plasma endothelin levels in humans after cardiac transplantation. Am J Cardiol 1991;67:752–4.
22. Stevenson LW, Tillisch JH, Hamilton M, et al. Importance of hemodynamic response to therapy in predicting survival with ejection fraction

≤20% secondary to ischemic or non-ischemic dilated cardiomyopathy. Am J Cardiol 1990;66:1348–54.

23. Hamilton MA, Stevenson LW, Child JS, Moriguchi JD, Walden J, Woo M. Sustained reduction in valvular regurgitation and atrial volumes with tailored vasodilator therapy in advanced congestive heart failure. Am J Cardiol 1991;67:259–63.
24. Vierhapper H, Wagner O, Nowotny P, Waldhausl W. Effect of endothelin-1 in man. Circulation 1990;81:1415–8.
25. Kiowski W, Luscher TF, Linder L, Buhler FR. Endothelin-1 induced vasoconstriction in humans. Circulation 1991;83:469–75.
26. The SOLVD Investigators. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. N Engl J Med 1991;325:293–302.
27. Cohn JN, Johnson G, Ziesche S, et al. A comparison of enalapril with hydralazine-isosorbide dinitrate in the treatment of chronic congestive heart failure. N Engl J Med 1991;325:303–10.
28. Watanabe T, Suzuki N, Shimamoto N, Fujino M, Imada A. Endothelin in myocardial infarction (letter). Nature 1990;344:114.
29. Fonarow GC, Chelimsky-Fallick C, Stevenson LW, et al. Effect of direct vasodilation vs angiotensin-converting enzyme inhibition on mortality in advanced heart failure: the Hy-C Trial. J Am Coll Cardiol 1992;19:842–50.